



## Complete Summary

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### GUIDELINE TITLE

The use of gabapentin and tricyclic antidepressants in the treatment of neuropathic pain in cancer patients: a clinical practice guideline.

### BIBLIOGRAPHIC SOURCE(S)

Librach L, Lloyd N, Jarvis V, Warr D, Jadad AR, Wilson J, Brouwers M, Wong R, Supportive Care Guidelines Group. The use of gabapentin and tricyclic antidepressants in the treatment of neuropathic pain in cancer patients: a clinical practice guideline. Toronto (ON). Cancer Care Ontario (CCO); 2006 Oct 11. 20 p. (Evidence-based series; no. 13-8). [27 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

## \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [May 2, 2007, Antidepressant drugs](#): Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

## COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

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## SCOPE

### **DISEASE/CONDITION(S)**

Neuropathic pain in cancer patients

### **GUIDELINE CATEGORY**

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Oncology  
Psychiatry  
Radiation Oncology

### **INTENDED USERS**

Advanced Practice Nurses  
Physicians

### **GUIDELINE OBJECTIVE(S)**

- To evaluate the roles of gabapentin and tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline) in terms of efficacy for pain relief and side effects in cancer patients with neuropathic pain
- To evaluate whether one is superior to the other

### **TARGET POPULATION**

Adult cancer patients experiencing neuropathic pain

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Gabapentin
2. Tricyclic antidepressants
  - Amitriptyline
  - Desipramine
  - Imipramine
  - Nortriptyline

## MAJOR OUTCOMES CONSIDERED

- Pain relief
- Paresthesia score
- Adverse effects

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

#### Literature Search Strategy

The MEDLINE database was searched from 1966 to November 2005 and CINAHL was searched from 1982 to November 2005 using treatment-specific text words and subject headings (gabapentin, neurontin, antidepressive agents, tricyclic, desipramine, imipramine, nortriptyline, amitriptyline) combined with the CAS registry number for gabapentin and combining these terms with those specific to study design and publication type (meta-analysis, randomized controlled trial(s), practice guideline). The Excerpta Medica database (EMBASE) was also searched up to November 2005 using agent-specific Emtree terms (gabapentin, tricyclic antidepressant agent). Those terms were then combined with the search terms for the following study design and publication types: practice guidelines, randomized controlled trials, systematic reviews, and meta-analyses.

Issue 4 (2005) of the Cochrane Library, Issue 4 (2005) of the Database of Abstracts of Reviews of Effects (DARE), and on-line conference proceedings from the American Society of Clinical Oncology (<http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Annual+Meeting+Summaries>; 1995-2005) were also searched. The Canadian Medical Association InfoBase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

#### Study Selection Criteria

##### *Inclusion Criteria*

Articles were eligible for inclusion in this systematic review of the evidence if they met all of the following criteria:

1. The study population included adult patients with neuropathic pain of any aetiology. Trials including cancer or non-cancer patients were considered eligible.
2. The article was a systematic review, meta-analysis, evidence-based practice guideline, or a fully published or abstract report of a randomized or non-randomized controlled trial.
3. The trial compared gabapentin versus one of four tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline) or the systematic review focused on the use of gabapentin and/or tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline).
4. One of the outcomes reported was pain relief. Other outcomes of interest were paresthesia score and adverse effects.

#### *Exclusion Criteria*

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

### **NUMBER OF SOURCE DOCUMENTS**

Two recent systematic reviews and two randomized trials were found and served as the primary evidence for this document.

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

### **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

It was decided not to pool the results of the trials because the eligible trials examined different measures of pain.

### **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

### **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Two systematic reviews, one focused on gabapentin and one on antidepressants including tricyclics, and two trials comparing the two agents against each other, were identified that met the inclusion criteria. There is an absence of large high-quality trials that focus on patients with cancer.

There is some evidence supporting a role for gabapentin in the treatment of neuropathic pain in general. In one systematic review and meta-analysis, the number needed-to-treat (NNT) to achieve relief was 4.3 in favour of gabapentin and 42% of patients in the gabapentin treatment group saw improvement in their pain compared with 19% in the placebo group. In the trial with cancer patients only, improvement with gabapentin versus placebo was found with some measures, including global pain scores and dysesthesia.

In addition, the other systematic review found global improvement and moderate improvement in neuropathic pain with tricyclic antidepressants compared to placebo. The number needed-to-treat to achieve at least moderate pain relief was 2 for amitriptyline and 2.1 for desipramine. In the only study focused specifically on reductions in cancer pain with tricyclic antidepressants, amitriptyline was found to significantly reduce pain compared to a placebo in 20 breast cancer patients.

In comparing gabapentin to tricyclic antidepressants, the evidence is not consistent. One study demonstrated superiority with gabapentin, and the second study did not detect a difference between the two treatments. A possible reason for the discrepant results could be that both trials were too small and inadequately powered to reliably detect significant differences between treatment groups on pain relief. In addition, one study was not blinded and, as with all non-blinded trials, patients are at higher susceptibility for bias with the answers they may provide regarding those treatments, thereby weakening the validity of the results and the ability to base clinical recommendations solely on those results.

The mean treatment effects detected for both amitriptyline and gabapentin were generally small but statistically significant; however, it is difficult to interpret the clinical significance of those benefits. The level of change in pain scores that represents a minimal clinically important difference (MCID) has been estimated at 1.5-2.2 on a 0-10 scale; however, the MCID varies by measurement scale and may vary according to baseline pain intensity. In addition, it is not currently possible to determine which patients will respond well to treatment and even small average improvements may translate into considerable benefits for individual patients; therefore, at the current time, statistically significant improvements in pain levels may also be considered clinically important.

Patient tolerance to both gabapentin and tricyclic antidepressants is generally good and adverse effects are moderate and manageable. Although amitriptyline is the only tricyclic antidepressant compared with gabapentin to date, there is evidence of benefit for other tricyclic antidepressants compared with placebo and the choice of treatment may depend on patient preferences and the medication side effect profiles. Data specific to patients with cancer are incomplete.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

### **Development and Internal Review**

This evidence-based series was developed by the Supportive Care Guidelines Group (SCGG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC). The SCGG comprises medical, radiation, and surgical oncologists; psychiatrists; palliative care physicians; nurses; radiation therapists; methodologists; administrators; a psychologist; and an anesthetist.

### **External Review by Ontario Clinicians**

Following review and discussion of Sections 1 and 2 of the original guideline document, the SCGG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

#### *Methods*

Feedback was obtained through a mailed survey of 122 health care providers in Ontario including 70 palliative care physicians, 22 psychiatrists, 18 nurses, 5 radiation therapists, 4 pharmacists, 2 family medicine specialists, and 1 medical oncologist. One member of the SCGG, a palliative care physician who was an author on the report, was included in the survey sample in error but was not included in the analysis. The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on February 1<sup>st</sup> and 2<sup>nd</sup> 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). In addition, the draft report and survey were distributed to attendees of the Cancer Care Ontario 2006 Signature Event (March 6<sup>th</sup>, 2006, Toronto), which was on palliative care. One attendee returned a survey and was included in the following analysis. The SCGG reviewed the results of the survey.

### **Report Approval Panel**

In December 2005, the evidence-based series report was reviewed by one member of the PEBC Report Approval Panel with expertise in clinical and methodology issues. The other Panel member contributed to the development of the report and was not eligible to provide feedback. Overall the report was

considered very well conceived, thoroughly researched, and likely to be helpful to clinicians.

The Panel member suggested that it would be beneficial to include a section in the report on issues related to outcome assessment and measurement specific to this topic, particularly in relation to the magnitude of benefit associated with pain assessment instruments. For example, where there are statistically significant differences between randomized groups in pain scores, is it possible to qualify what these differences mean to a patient? Does a number needed-to-treat (NNT) of 2 reflect mild pain reduction or eradication of pain? Although outcome assessment is a complex topic in its own right, readers would benefit from the SCGG interpretation of magnitude.

In addition, the Panel member also suggested that expert advice on dose, schedule, and duration of therapy would be helpful. Although such recommendations would be informed by the evidence rather than strictly evidence-based, readers may benefit from the SCGG expertise.

The feedback from the Report Approval Panel was consistent with that received through the external review process. In response, the SCGG added further discussion of the complexity of pain assessment and the evaluation of clinically important differences, and have included a Qualifying Statement on medication dosing, based on clinical expertise and the trials reviewed in the report. The Report Approval Panel formally approved the Evidence-based Series Report in October 2006.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- Gabapentin or tricyclic antidepressants are recommended as options for the treatment of neuropathic pain in cancer patients.
- While there is limited evidence comparing different tricyclic antidepressant drugs with this population, amitriptyline has been shown to have some beneficial effect, although the tolerability of that agent may be a concern with some patients. In the opinion of the Supportive Care Guidelines Group, other tricyclic antidepressants may be expected to have similar efficacy as amitriptyline with fewer side effects.
- There is insufficient evidence demonstrating the superiority of either gabapentin or tricyclic antidepressants over the other in neuropathic pain management.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by systematic reviews and randomized trials.

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

- The randomized trials were comprised of a combined total of 50 patients with diabetic neuropathy and compared gabapentin to amitriptyline. In one open-label randomized trial, patients allocated to receive gabapentin experienced significantly greater pain reduction compared to those in the amitriptyline group (mean change in pain intensity 1.9 versus 1.3 points below baseline;  $p=0.026$ ). Side effects were also less severe in the gabapentin arm. Alternatively, no significant differences in pain relief or overall side effects were detected between gabapentin and amitriptyline in a double-blind randomized crossover trial.
- One systematic review examined the utility of gabapentin through 14 reports of 15 studies which had a combined total of 1468 patients. Data from a synthesis of seven studies found greater reductions in pain scores for patients receiving gabapentin compared to a placebo (42% versus 19% of patients, respectively, experienced pain relief). In the only trial comparing gabapentin to a placebo among 121 patients with neuropathic pain due to cancer, the reduction in mean global pain scores was also found to be greater among those allocated to gabapentin compared to a placebo (mean follow-up pain score, 4.6 versus 5.4,  $p=0.025$ ). No significant differences in adverse events were found between groups.
- The other systematic review examined the effect of antidepressants on pain through 50 trials which included a combined total of 2515 patients. Fourteen of the 25 placebo-controlled studies that examined the effect of tricyclic antidepressants on pain used measures of global improvement or moderate improvement; patients in the tricyclic antidepressant group experienced significantly greater pain reduction. In one small trial focusing solely on cancer patients, amitriptyline was found to significantly reduce pain compared to a placebo in 20 breast cancer patients (median post-treatment pain intensity on a visual analogue scale: 0.2 versus 3.1, at the breast scar and 0.5 versus 5.0, in the arm).

### **POTENTIAL HARMS**

#### **Gabapentin**

Adverse effects were inconsistently reported in the studies and the review did not provide detailed data, but the relative frequencies were given as: dizziness 24%, somnolence 20%, headache 10%, diarrhea 10%, confusion 7%, and nausea 8%. The number needed-to-harm (NNH) for adverse events leading to withdrawal from a trial was not significant (assessed across five trials) and for minor harm was 3.7 (95% confidence interval [CI], 2.4-5.4) based on data from two trials.

#### **Gabapentin versus Tricyclic Antidepressants**

- There were no dropouts in one reported trial. In that trial, a statistically significant difference between groups was detected in the overall frequency of

side effects favouring gabapentin (4 patients versus 11 patients,  $p=0.003$ ). The most common adverse effects were dizziness, somnolence, constipation, and dry mouth.

- In the other trial, four patients withdrew because of adverse effects, protocol violation, or voluntary withdrawal (2 under each treatment), and three were crossed over early because of intolerable side effects or pain (2 while receiving gabapentin and one while receiving amitriptyline). A total of 19 patients completed both six-week treatment periods. Eighteen patients receiving gabapentin and 17 patients receiving amitriptyline experienced adverse effects. With the exception of weight gain, which was more frequent with amitriptyline ( $p=0.01$ ), no statistically significant differences in adverse effects were detected between treatment groups ( $p>0.05$ ). The most prevalent adverse effects were sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia, and lethargy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Evidence for the effectiveness of gabapentin compared with tricyclic antidepressants in cancer populations is limited to two small trials; however, evidence from non-cancer populations was also considered in the development of the guideline and supports the recommendations.
- Given the complexity of assessment of pain syndromes in cancer patients, it is the opinion of the Supportive Care Guidelines Group that individual patient assessment should determine the appropriate treatment option and gabapentin and tricyclic antidepressants may be used alone, sequentially, or with other analgesic agents, including opioids, in the treatment of neuropathic cancer pain.
- Evidence on treatment dosing was not systematically reviewed; however, in the expert opinion of the Supportive Care Guidelines Group, the doses commonly used in clinical practice and represented in the trials included in the systematic review are reasonable options.

*Gabapentin:* starting total daily dose of 300-600 milligrams (mg), titrating up by 300 mg every 5-7 days until patient pain is significantly reduced, intolerable adverse effects occur, or a maximum daily dose of 2400 mg is reached.

*Tricyclic antidepressants:* starting daily dose of 10-25 mg, titrating up until patient pain is significantly reduced, intolerable adverse effects occur, or a maximum daily dose of 100 mg is reached.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Librach L, Lloyd N, Jarvis V, Warr D, Jadad AR, Wilson J, Brouwers M, Wong R, Supportive Care Guidelines Group. The use of gabapentin and tricyclic antidepressants in the treatment of neuropathic pain in cancer patients: a clinical practice guideline. Toronto (ON). Cancer Care Ontario (CCO); 2006 Oct 11. 20 p. (Evidence-based series; no. 13-8). [27 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2006 Oct

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### SOURCE(S) OF FUNDING

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care  
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## **GUIDELINE COMMITTEE**

Supportive Care Guidelines Group

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

The authors disclosed potential conflicts of interest relating to the topic of this report. No potential conflicts were declared.

## **GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

None available

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI on March 28, 2008.

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Date Modified: 9/22/2008

